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REVIEW

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Kinetic modeling for blood purification in critical care: this article is based on a study first reported in kidney and dialysis (in Japanese)

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Abstract

Background: In blood purification therapies for critical care, there are no guidelines for selecting modalities of the treatment or for determining the treatment schedule, treatment time, and operating conditions, such as dialysate flow rate (Q_D) and filtration flow rate (Q_F). In this paper, the solute removal characteristics of blood purification for critical care and the optimal operating conditions for individual patients are discussed from the viewpoint of kinetic modeling.

Method: An in vitro study using an aqueous solution involving several marker solutes was performed.

Results: From a result of the continuous hemodialysis (CHD) experiments, the Q_D should be required at least twice the patient's blood flow rate (Q_B) for sufficient removal of small molecular substances. CHD is of limited use for the removal of middle-sized molecules. During the continuous hemofiltration (CHF) experiments in the post-dilution mode, the maximum Q_F value can be determined as about 1/4 of the Q_B because of the existence of the formed elements. In summary of the continuous hemodiafiltration (CHDF) experiments, the Q_F is about 1/4 of Q_B value and the Q_D should be set up at least twice the Q_B value.

The determination of adequate operating conditions for individual patients can be summarized from a kinetic modeling viewpoint:

1. Determination of the targeted solute according to the patient's state.
2. Determination of the generation rate of the targeted solute by collecting spent dialysate and/or filtrate.
3. Determination of the minimal requirement treatment dose from the actual and targeted solute concentration levels.
4. Choice of treatment modality and determination of the treatment time according to the clearance value.

Conclusions: Measurement of the removed amount of solute by collecting the spent dialysate and/or filtrate is recommended to maintain an adequate plasma level of the targeted solute of patients, who often have unstable states. The adequate operating conditions for each patient can be determined from a kinetic modeling viewpoint.

Keywords: Kinetic modeling, Compartment model, Adequate operating conditions

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Background

In blood purification therapies for critical care, there are no guidelines for selecting modalities, such as continuous hemodialysis (CHD), continuous hemofiltration (CHF), and continuous hemodiafiltration (CHDF), or for determining the treatment schedule, treatment time, and the operating conditions, such as the blood flow rate (Q_B), dialysate flow rate (Q_D), and filtration flow rate (Q_F), for individual patients. Instead, these conditions are determined according to the experience of the patient's doctor based on trial and error.

In this paper, the solute removal characteristics of blood purification for critical care and the optimal operating conditions for individual patients are discussed from the viewpoint of kinetic modeling.

Solute removal characteristics of blood purification devices

Blood purification therapy for critical care requires some specific conditions, compared with maintenance dialysis therapy for chronic kidney disease patients:

- (1) A lower Q_B is needed because the patient often has an unstable hemodynamic state and is unlikely to have an arteriovenous fistula (AVF) or arteriovenous graft (AVG).
- (2) A longer treatment time is required because of the lower Q_B .
- (3) The patients are often actively bleeding.

Blood purification devices for critical care require the following characteristics:

- (1) A compact size with a smaller priming volume (PV)
- (2) A lower degradation for device performance
- (3) A lower pressure drop on the blood side to avoid clotting in the device

Based on these requirements, a relatively small size of hollow fiber membrane device with a membrane surface area (A) of 0.1–1.1 m², a PV of 12–87 mL, and a slightly larger inner diameter of the hollow fiber (220 μm) has been developed and used clinically.

To determine the solute removal characteristics of CHD, CHDF, and CHF, an in vitro study using an aqueous solution and a cellulose triacetate membrane filter, FB-50H, with an A of 0.5 m² (Nipro Corp, Osaka, Japan) was performed [1]. Reverse osmosis (RO) water including solutes was used for the blood side solution in all the experiments, and RO water was used for the dialysate in the HD and HDF experiments. Urea (60 Da), creatinine (113 Da), vitamin B₁₂ (1350 Da), and inulin (5200 Da) were chosen as

marker solutes in this study. Samples of the solute concentrations at the inlet and outlet of the blood side (C_{BI} and C_{BO}) and at the outlet side of the dialysate (C_{DO}) for CHD or CHDF and at the filtrate side (C_F) for CHF were obtained. All the experiments were performed using a multipurpose dialysis machine (ACH-07; Asahikasei Medical Co. Ltd., Tokyo, Japan).

The solute clearances were calculated using the following equations:

- (1) Blood side clearance (K_B) for all experiments:

$$K_B = \frac{C_{BI} - C_{BO}}{C_{BI}} Q_{BI} \quad (1)$$

- (2) Dialysate side clearance (K_D) for the CHD and CHDF experiments:

$$K_D = \frac{C_{DO}}{C_{BI}} Q_{DO} \quad (2)$$

- (3) Filtrate side clearance (K_F) for the CHF experiments:

$$K_F = \frac{C_F}{C_{BI}} Q_F = SC \cdot Q_F \quad (3)$$

SC is the sieving coefficient of the solute.

The left side of Fig. 1 shows the effects of Q_B on K_D in the CHD experiments under a Q_D of 48.3 mL/min with no filtration [1]. The K_D values for urea and creatinine increased with the Q_B . The right side of Fig. 1 shows the effects of Q_D on K_B in the CHD experiments under a Q_B of 50.0 mL/min with no filtration [1]. The K_B value increased steeply with Q_D under a $Q_D < 100$ mL/min and reached a plateau level at a Q_D of over 200 mL/min. Although a Q_D of 500–1500 mL/h was chosen from an economical viewpoint in a typical clinical treatment, Q_D should be required at least twice the Q_B for the sake of obtaining sufficient K_B value. On the other hand, the vitamin B₁₂ and inulin K_B values were less than half of the urea and creatinine K_B values. Thus, CHD is of limited use for the removal of such middle-sized molecules.

Figure 2 shows the effect of Q_F on K_F in the CHF experiments using a post-dilution mode under a Q_B of 50.0 mL/min with no dialysate flow [1]. The K_F value increased proportionally with the Q_F . From Eq. 3, the slope of the proportional line indicates the

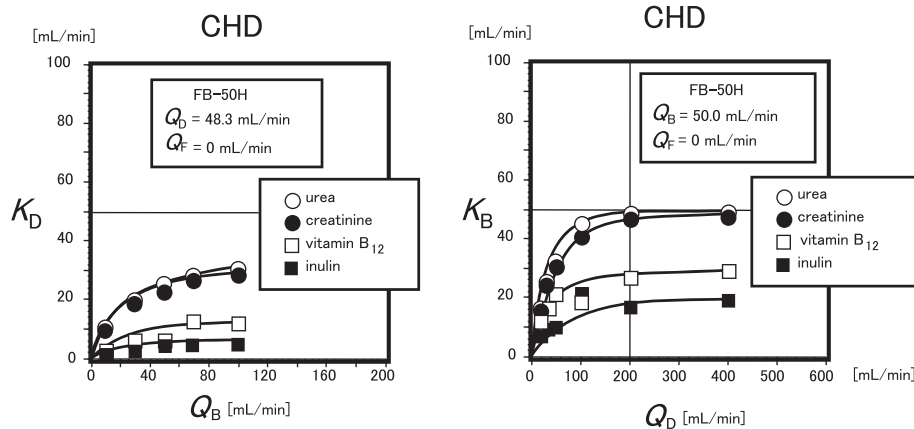


Fig. 1 Effects of blood flow rate (Q_B) and dialysate flow rate (Q_D) on solute clearance (K) in the CHD experiments [1]

SC value of the solute to the membrane device. Because the solute SC value is almost unchanged for a device, the K_F value strongly depends on the Q_F (namely, the amount of replacement fluid, V_R). In the post-dilution mode, the maximum Q_F value can be determined as about 1/4 of the Q_B because of the existence of formed elements, such as erythrocytes.

Figure 3 shows the effects of Q_D and Q_F on K_B in the CHDF experiments using a post-dilution mode under a Q_B of 50.0 mL/min [1]. As shown on the left

side of Fig. 3, the relationship between the K_B and Q_D values was similar to that observed in the CHD experiments. The K_B values for vitamin B₁₂ and inulin, however, slightly increased as a result of convective transport arising from a Q_F of 10.4 mL/min. On the other hand, as shown on the right side of Fig. 3, a high efficiency of solute removal was obtained using both diffusive and convective transport in HDF using the post-dilution mode.

In summary, the Q_F is about 1/4 of the Q_B value, and the Q_D should be set at least twice the Q_B value during CHDF treatment.

Optimal operating conditions for blood purification therapies for critical care

Determining the operating conditions for individual patients is very important for clinical treatment. An adequate V_R and Q_D can be determined from a kinetic modeling viewpoint. In this paper, the adequate parameters were determined using urea kinetic modeling [2].

If a 1-compartment model is used to describe urea transport during continuous renal replacement therapies (CRRT) such as CHD, CHE, and CHDF, the plasma solute concentration (C) can be described as follows:

$$C = \frac{G}{K_{av}} = \frac{GT}{Kt} = \left(\frac{G}{K}\right) \times \left(\frac{T}{t}\right) = \left(\frac{GT}{V}\right) \times \left(\frac{V}{Kt}\right) \quad (4)$$

where the symbols G and K_{av} denote the urea generation rate and the time-averaged urea clearance, respectively. The C can be defined as G divided by K_{av} . After the Kt and T in this equation, C can be described as GT/V divided by Kt/V . The symbols t and T represent the

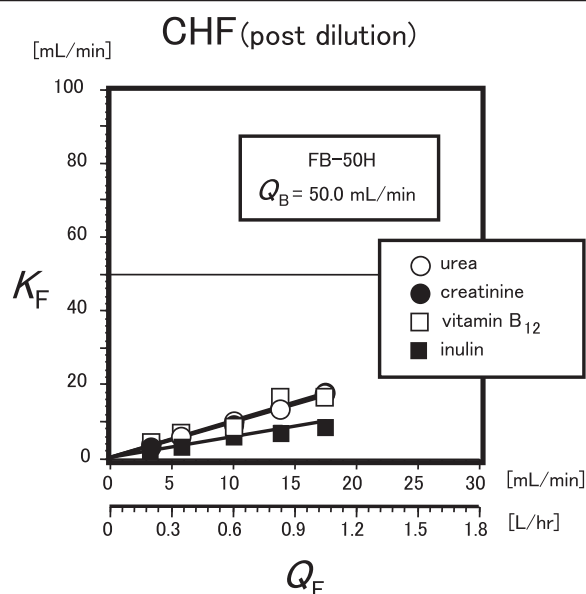


Fig. 2 Effects of filtration flow rate (Q_F) on solute clearance (K) in the CHF experiments [1]

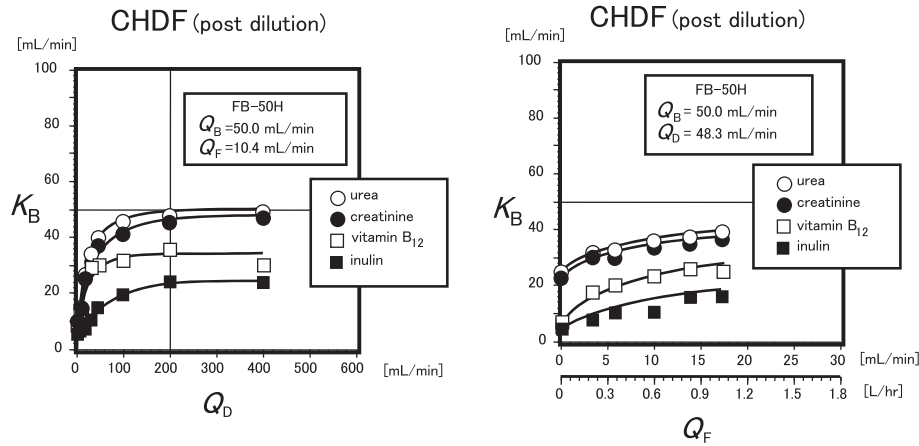


Fig. 3 Effects of dialysate flow rate (Q_D) and filtration flow rate (Q_F) on solute clearance (K) in the CHDF experiments [1]

treatment time and the treatment cycle (for example, 24 h). The V denotes the urea distribution volume.

Material balance equations for urea can be applied as follows:

$$M_G = GT \quad (5)$$

$$M_R = Kt \times C_{av}, \quad (6)$$

where the symbols M_G and M_R denote the amount of urea generated and removed by CRRT, respectively. C_{av} means the time-averaged concentration of urea. The relations among M_G , M_R , and C_{av} can be described using the following 3 patterns:

- (1) When $M_G > M_R$ for T , the C increases because the generation rate is superior to the removal rate.
- (2) When $M_G = M_R$ for T , the C remains unchanged because the generation rate is equal to the removal rate.
- (3) When $M_G < M_R$ for T , the C decreases because the removal rate is superior to the generation rate.

The change in the urea concentration, ΔC , can be described as follows:

$$\Delta C = \frac{M_G - M_R}{V} \quad (7)$$

By substituting Eqs. 5 and 6 into Eq. 7, the following equations can be obtained:

$$M_G = M_R + V\Delta C \quad (8)$$

$$G = (M_R + V\Delta C)/T \quad (9)$$

As shown in Eqs. 8 and 9, the urea generation rate G can be estimated by measuring the amount of urea

removed by the CRRT treatment M_R and the change in the urea concentration ΔC for T .

As an example, we supposed that a patient weighing 50 kg (BW) received a CRRT treatment and the BUN level of the patient increased from 80 to 100 mg/dL for 24 h. If the M_R was obtained by collecting the spent dialysate and filtrate during the treatment and estimated as 5000 mg, the G value of the patient can be calculated as follows using Eq. 9 and supposing V (L) to be 60 % of the BW (kg):

$$G = \frac{5000 + (50 \times 0.6) \times 10 \times (100 - 80)}{60 \times 24} = 7.6 \text{ mg/min}$$

We can determine the optimal operating conditions of the CRRT treatment for the patient using urea kinetic modeling.

The amount of urea generated during 24 h can be estimated as follows:

$$GT = 7.6 \times 60 \times 24 = 11,000 \text{ mg} = 11 \text{ g}$$

If the target of the BUN level is supposed to be 80 mg/dL, the minimal requirement of the treatment dose can be calculated using Eqs. 5 and 6 as follows:

$$Kt = 11,000/80 = 137.5 \text{ dL} = 13.8 \text{ L}$$

From this estimation, the optimal operating conditions for several blood purification therapies can be determined as follows:

- (1) CHF: The minimal amount of replacement fluid (V_R) is 14 L.
- (2) CHD: When the dialyzer clearance (K) is assumed to be 30 mL/min, the treatment time can be calculated as follows:

$$13.8 \times 1000/30 = 458 \text{ min} = 7.6 \text{ h.}$$

- (3) CHDF: When the dialyzer clearance (K) is assumed to be 40 mL/min, the treatment time can be calculated as follows:

$$13.8 \times 1000/40 = 343 \text{ min} = 5.7 \text{ h.}$$

Although urea removal in CRRT therapies was mentioned above, CHDF and CHF (which are based on convective transport by filtration) are effective for the removal of relatively large molecules, such as some kinds of cytokines.

The determination of adequate operating conditions for individual patients who receive blood purification therapy for critical care can be summarized from a kinetic modeling viewpoint as follows:

1. Determination of the targeted solute according to the patient's state.
2. Determination of the generation rate of the targeted solute by collecting spent dialysate and/or filtrate.
3. Determination of the minimal requirement treatment dose from the actual and targeted solute concentration levels.
4. Choice of treatment modality and determination of the treatment time according to the clearance value K .
 - 4-1 In CHF, the replacement volume V_R can be determined as $V_R = Kt$. The filtration flow rate Q_F , which is identical to K , can be estimated as 15–30 % of the blood flow rate Q_B . The treatment time t can be determined by Kt/K ($= V_R/Q_F$).
 - 4-2 In CHD, the dialysate flow rate Q_D should be set at least twice the Q_B . The t can be determined by Kt/K .
 - 4-3 In CHDF, the Q_F and Q_D should be shared according to the targeted solute. The Q_D should be set at least twice the Q_B . The t can be determined by Kt/K .

Conclusions

Measurement of the removed amount of solute by collecting the spent dialysate and/or filtrate is recommended to maintain an adequate plasma level of the targeted solute in critical care patients, who often have unstable states.

Competing interest

I declare that there are no conflicts of interest with any companies regarding this study.

Author's contributions

MM carried out this study and drafted the manuscript.

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